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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GRUN, JAMES LESLIE

ART UNIT	PAPER NUMBER
1641	9

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/890,442	KARL et al.
Examiner	**Art Unit**
James L. Grun, Ph.D.	1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 20-140 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 20-140 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☒ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached ~~detailed Office action~~ for a list of the certified copies not received: 199 11 044.1 not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claims 134-138 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809.

It is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated M 10.1.11 and M 13.4.14 are known and publicly available, or can be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies necessary to practice the instant invention

or filing of evidence of deposit is required. Without a publicly available deposit of the above cell lines, one of skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: the claimed cell line; the cell lines which produce the chemically and functionally distinct antibodies claimed; and/or, the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Therefore, it would require undue experimentation to reproduce the claimed monoclonal antibody species chemically as produced by the hybridomas designated M 10.1.11 and M 13.4.14. A suitable deposit of the hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See the criteria set forth in 37 CFR §§ 1.801-1.809.

If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty, that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the biological materials will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in 37 CFR §§ 1.801-1.809, applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposits will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) the deposits were viable at the time of deposit; and,

(e) the deposits will be replaced if they should ever become non-viable.

Claims 20-140 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant provides multiple definitions of what is encompassed by the term "NT-proBNP", such as all peptides, irregardless of structure, which are bound in applicant's assay (see e.g. page 6), or only that peptide consisting of amino acids 1-76 of an unspecified proBNP sequence (page 10). Applicant provides sketchy details regarding the cloning of the NT-proBNP and provides no guidance whatsoever to relevant starting materials or how the primers were used such that one could readily reproduce the cloning and envision what structure it was that applicant cloned. There are many structurally different BNP fragments and proBNP sequences in many different animal

species and applicant sets forth no particular structure encompassed by the term "NT-proBNP" which would allow one to envision what structure functions in the invention as disclosed. Adequate written description requires more than a mere statement that a molecule is part of the invention and a reference to a potential method of isolating it. The molecule itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of molecules by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules, usually defined by a sequence, falling within the scope of the claimed genus. Absent further written description and guidance from applicant, one would not know which sequences or structures were part of the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 31, 38-73, 77, 86, 93-129, 136, and 140 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 22 and claims 31, 40, 49, 58, 67, 77, 86, 95, 104, 113, and 122 dependent thereupon, it is not clear what properties are encompassed by "bind simultaneously" because it is not clear if applicant intended a temporal parameter or a localization limitation.

In claims 38-55 and claims 56-73 and 93-128 dependent thereupon, "using" is not a proper method step. The examiner would suggest --with--.

In claim 129, the interrelationships of the steps and components of the method are not clear.

Claim 136 is vague and indefinite in the recitation of "the antibody...is equivalent" because it is not clear what applicant intends as encompassed or excluded. Without a clear and unambiguous description and recitation of "equivalent" and how one performs a comparison therefor, the metes and bounds of the invention as claimed cannot be determined.

In claim 140, the interrelationships of the steps and components of the method are entirely unclear. There is no connection between immunizing an organism and selecting clones. The recitation of "the antibodies" lacks antecedent basis.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 130-131 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. There is no indication that the product(s) as claimed are isolated and no claimed degree of purity for the product(s) which would indicate "the hand of man". Thus, the products as claimed are considered a product of nature which is non-statutory subject matter.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-28, 38-46, 74, 129-133, 136, and 139 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Hall (U.S. Pat. No. 5,786,163).

Hall teaches the immunization of animals with the N-terminal fragment of human brain natriuretic peptide prohormone, BNP(1-76) (NT-proBNP), or fragments thereof for the elicitation of polyclonal or monoclonal antibodies specifically binding thereto (e.g. col. 4, lines 1-15; Example 1). The reference teaches sandwich assays for the determination of BNP(1-76) in samples of body fluids, in particular from patients suffering from heart disease, wherein immobilized antigen-specific monoclonal or polyclonal antibodies capture antigen and directly or indirectly labelled second antibodies, which may be monoclonal or polyclonal, detect bound antigen (e.g.: col. 2; claims 1 and

7-9). The reference exemplified monoclonal and polyclonal antibodies to the antigen, in particular to fragments BNP(1-21), BNP(22-46), or BNP(47-64). The reference teaches the use of the full length N-terminal fragment, BNP(1-76), made by using techniques well known in the art (e.g. col. 3, lines 61-67). There is nothing on the record which serves to distinguish a recombinantly made BNP(1-76) peptide from the peptide made or isolated by an alternative means.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 20-74, 129-133, 136, and 139 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hall (U.S. Pat. No. 5,786,163) in view of Hunt et al. (Clin. Endocrinol. 47: 287, 1997).

The teachings of Hall are as set forth previously and differ from the invention as instantly claimed in not teaching assays of patients suffering from heart disease of particular NYHA classes and in not teaching detection of BNP(1-76) at levels of 1 picomolar.

Hunt et al. teach that levels of NT-proBNP (BNP(1-76)) were in the picomolar range for normal subjects and that higher levels of NT-proBNP were detected in patient plasma samples with increasing cardiac impairment as classed in NYHA classes I-III.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have optimized the immunoassays of Hall for detection of antigen in the picomolar range because this is taught by Hunt et al. as necessary for determinations of NT-proBNP antigen concentration in the normal population and one would have been motivated to optimize the assay to detect antigen in the concentration range known for the antigen in biological fluid samples. One would have had a reasonable expectation of success since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233. It would have been further obvious to have used the assay results of Hall, as modified, to differentiate patients with different degrees of cardiac impairment, such as into the NYHA classes taught by Hunt et al., because increasing levels of NT-proBNP was known to be a marker indicative of increasing cardiac impairment as taught by either of Hall or Hunt et al.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 20-133, 136, and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hall (U.S. Pat. No. 5,786,163) in view of Hunt et al. (Clin. Endocrinol. 47: 287, 1997) as applied to claims 20-74, 129-133, 136, and 139 above, and further in view of Seilhamer et al. (WO 89/12069) and Sudoh et al. (Biochem. Biophys. Res. Comm. 159: 1427, 1989).

The teachings of Hall, as modified by Hunt et al., are as set forth previously and differ from the invention as instantly claimed in not teaching recombinant production of NT-proBNP (BNP(1-76)) for use and in not teaching the inclusion of unlabelled BNP(1-76) in an immunoassay kit as standard.

Seilhamer et al. teach the genomic sequence of prepro and pro forms of human natriuretic-related peptide (NRP) (Figs. 5 and 6), which are those of preproBNP and proBNP in view of the cDNA sequence taught for preproBNP and proBNP by Sudoh et al. (Fig. 2). Seilhamer et al. teach that these peptides, or any encoded subsegment, can be produced in a variety of ways, including using recombinant methods, and set forth the details of such methods (pages 20-27).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have recombinantly produced BNP(1-76) for use in the methods and kit of Hall, as modified, because Hall desires the use of full length BNP(1-76) for immunization and immunoassay methods, and teaches that the peptide can be made by using techniques well known in the art, and Seilhamer et al. teach that recombinant methods, in addition to solid-phase synthesis, can be used for the production of the BNP peptides or any subsegment thereof and provides methodological details therefor. One would have had obvious motivation to substitute recombinant methods for

solid-phase synthesis in Hall, as modified, for making BNP(1-76) in view of the direct suggestion in Seilhamer et al. to do so for the benefits taught therein. It would have been obvious to one of ordinary skill in the art that a labelled antigen was not required for performance of the sandwich immunoassay for BNP(1-76) in Hall, as modified, and one would have been motivated to provide an unlabelled antigen in a kit and assay therefor to obviate the extra and unnecessary step of labelling antigen and because the use of a standard for determination of unknown quantities in a sample is notoriously old and well known in the art and one would have been motivated to provide a standard antigen as related to the target NT-proBNP antigen as possible.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hall (WO 93/24531) contains disclosure essentially identical to Hall (U.S. Pat. No. 5,786,163).

Ng et al. (WO 00/35951) teach detection of an epitope in amino acids 65-76 of NT-proBNP for diagnosis of left ventricular dysfunction.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (703) 308-3980. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (703) 305-3399.

The phone numbers for official facsimile transmitted communications to TC 1600, Group 1640, are (703) 872-9306, or (703) 305-3014, or (703) 308-4242. Official After Final communications, only, can be facsimile transmitted to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. The above inquiries, or requests to supply missing elements from Office communications, can also be directed to the TC 1600 Customer Service Office at phone numbers (703) 308-0197 or (703) 308-0198.

James L. Grun, Ph.D.
September 27, 2003

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641